

Exhibit H

ONLINE FIRST

Prevalence of Fracture and Fragment Embolization of Bard Retrievable Vena Cava Filters and Clinical Implications Including Cardiac Perforation and Tamponade

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Background: Vena cava filters represent an alternative treatment option for patients with contraindications to anticoagulation, or they might serve as adjunctive treatment for continued emboli despite anticoagulation. The fracture of a filter strut with subsequent end-organ embolization is a rarely reported but potentially life-threatening occurrence.

Methods: We sought to determine the prevalence of fracture and embolization of the Bard Recovery (first generation) and the Bard G2 (second generation) vena cava filters. A retrospective, single-center, cross-sectional study was conducted by evaluating all patients who received either a Bard Recovery or Bard G2 filter from April 2004 until January 2009. A total of 189 patients had undergone implantation: 1 pregnant woman and 35 patients who died were excluded from our study. In addition, 10 patients who had the filter removed were also excluded. Ultimately, 80 patients participated in the trial. Subjects underwent fluoroscopy to assess the filter's integrity. Embolized struts were localized by fluoroscopy. Echocardiography and cardiac computed tomography were per-

formed in patients with fragment embolization to the heart.

Results: Thirteen of 80 patients had at least 1 strut fracture (16%). At least 1 strut in 7 of the 28 Bard Recovery filters fractured and embolized (25%). In 5 of these 7 cases, patients had at least 1 fragment embolize to the heart (71%). Three patients experienced life-threatening symptoms of ventricular tachycardia and/or tamponade, including 1 patient who experienced sudden death at home. Six of 52 Bard G2 filters fractured (12%). In 2 of these 6 cases, the patients had asymptomatic end-organ fragment embolization.

Conclusion: The Bard Recovery and Bard G2 filters had high prevalences of fracture and embolization, with potentially life-threatening sequelae.

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VENOUS THROMBOEMBOLISM occurs in more than 200 000 US citizens per year.¹ Anticoagulation is the standard therapy for these patients. Vena cava filters have been used as an alternative therapy for patients who have contraindications to anticoagulation or as adjunctive treatment in patients with continued emboli despite anticoagulation.

See Invited Commentary at end of article

Widely recognized complications from filter placement have included erosion through the vena cava wall, visceral perforation, and filter thrombosis, obstruc-

tion, and migration. Fracturing of a filter strut with subsequent migration to the heart is a rarely reported occurrence.

The Bard Recovery filter (Bard Peripheral Vascular, Tempe, Arizona) was developed as a permanent but potentially retrievable filter and was commercially available from April 2003 until October 2005. The basic design of the filter's construction (**Figure 1 A**) consists of 2 levels of 6 radially distributed nitinol arms and legs that anchor the filter into the inferior vena cava and serve to trap any embolizing clot.

A patient was seen at our institution more than 3 years after filter placement with pleuritic chest pain, cardiac tamponade, and perforation of the right ventricle as a result of filter fragmentation and embolization. The patient underwent emergency open-heart surgery for removal of

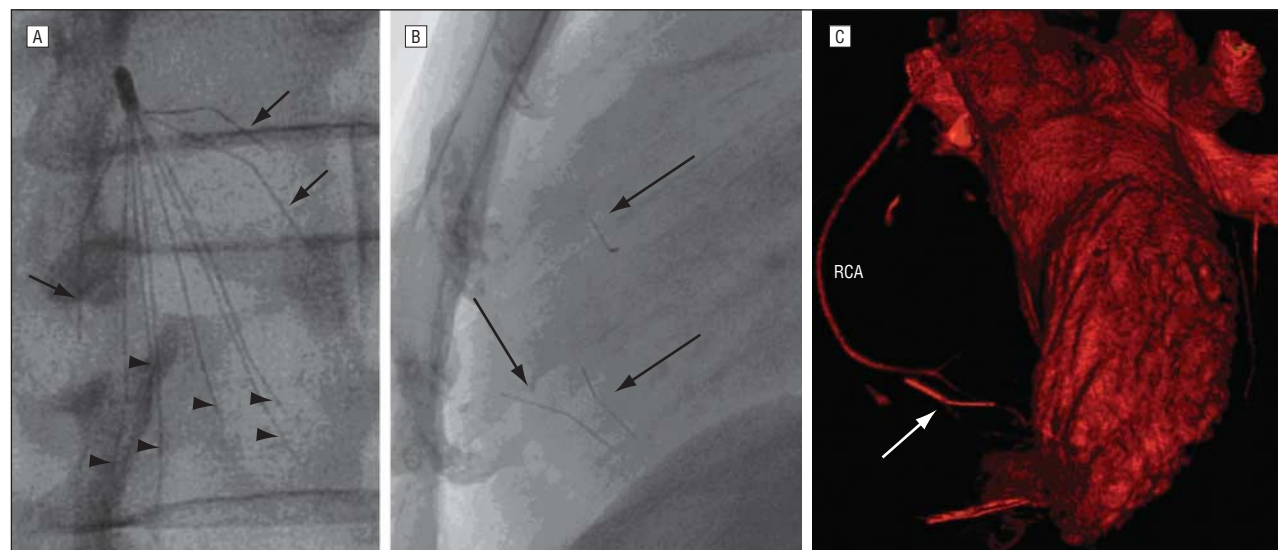


Figure 1. Bard Recovery vena cava filter (Bard Peripheral Vascular, Tempe, Arizona) implanted in patient 2. A, Fluoroscopic image of the filter showing 3 of the 6 radial nitinol arms attached to the cava filter (arrows) and all 6 radial nitinol legs still attached to the cava filter (arrowheads). B, The 3 arms missing from the filter in panel A are clearly seen on fluoroscopy of the heart (arrows). C, Computed tomographic image showing an embolized filter fragment (arrow) that missed perforating the right coronary artery (RCA) by less than 1 cm.

Table 1. Characteristics of the 80 Patients Who Underwent Bard Vena Cava Filter Implantation^a

Characteristic	Bard Filter Implanted	
	Recovery (n=28)	G2 (n=52)
Patient age, mean (SD), y	56.2 (17.5)	48.5 (17.7)
Men, No. (%)	14 (50)	28 (54)
Duration of implantation, mean (SD), mo	50.2 (4.9)	23.5 (8.3)
Implanting physicians, No.	6	21
Indications for implantation, No. (%) ^b		
Unknown	1 (4)	17 (33)
Trauma	7 (25)	10 (19)
DVT/PE	12 (43)	5 (10)
Warfarin intolerance	1 (4)	4 (8)
Surgery prophylaxis	6 (21)	15 (29)
Malignant neoplasm prophylaxis	1 (4)	1 (2)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary emboli.

^aThe receiving patient's age, duration of months from implantation until follow-up fluoroscopy, number of different implanting physicians and indications for implantation are reported for patients receiving the Recovery filter and the G2 filter. "Recovery" and "G2" are proprietary names of vena cava filters manufactured by Bard Peripheral Vascular, Tempe, Arizona.

^bPercentages do not total 100% owing to rounding.

the fractured fragments and drainage of the pericardial effusion.

In September 2005, Bard modified the design of the Bard Recovery filter to improve fracture resistance by reducing stress concentration at the apex of the filter using longer arms with curved ends to reduce the load to the arms as they exit the apex. This new design was labeled and marketed as the Bard G2 cava filter, replacing the initial Bard Recovery filter. Over 65 000 Bard G2 filters have been implanted since September 2005.

Based on our institution's herald case and the limited case reports in the literature, we undertook a retrospective review of all patients at our institution who received the Bard Recovery filter or Bard G2 filter.

METHODS

The institutional review board approved this study. Retrospective review of the procedure logs was used to identify all patients who received a Bard Recovery or Bard G2 filter from April 2004 until January 2009. We attempted to contact all nonpregnant living patients at their last known places of residence. Patients were asked to submit to fluoroscopy of the filter to assess its integrity. If a device had fragmented, all embolized nitinol arms or legs were localized on fluoroscopy, and their locations were recorded. Transthoracic echocardiography was performed in all patients who had fragment embolization to the heart. Selected patients with embolization to the heart also underwent cardiac computed tomography to further define the exact location of the fragments.

RESULTS

A total of 189 patients underwent implantation of the Bard Recovery or Bard G2 vena cava filter at our institution between 2004 and 2009, usually as treatment for deep-vein thrombus or pulmonary embolus (**Table 1**). Because the Bard Recovery filter was first on the market and was later replaced by the Bard G2, the duration of time between filter implantation and fluoroscopy for the Bard G2 filter is shorter than that of the Bard Recovery filter.

Thirty-five of the 189 patients with Bard filters had died by the time of the study; 10 others had undergone routine scheduled prophylactic recovery of their filter; and 1 was pregnant and could not undergo fluoroscopy. Attempts were made to contact the remaining 143 patients by letter and telephone, and 84 patients were contacted, of whom 80 agreed to participate in the trial. After informed consent, all 80 patients underwent fluoroscopy of the device. The patient enrollment flowchart is shown in **Figure 2**. Thirteen of the 80 patients who underwent fluoroscopy were found to have at least 1 nitinol arm or leg fracture (16%). The average age for

this group was 48.9 years, and the device was evaluated, on average, 37.8 months after implantation (**Table 2**).

The subset of patients who had received the Bard Recovery filter had a 25% prevalence of device fragmentation and embolization (7 of 28). All Bard Recovery filter fractured fragments embolized via the venous system from the inferior vena cava (IVC) to an end organ. Five of the 7 fractured devices had at least 1 fragment embolize and come to rest in the right ventricle of the heart (71%). Two of these patients experienced symptoms of pleuritic chest pain with documented nonsustained ventricular tachycardia. Three months after completion of this study, 1 of these 2 patients experienced sudden death at home. Included in this group is the patient who experienced hemorrhagic pericardial effusion with subsequent cardiac tamponade requiring emergency open-heart surgery with drainage and fragment removal. In total, 6 of 7 patients who experienced fracture of a Bard Recovery filter (86%) had a fragment either embolize and come to rest in the right ventricle of the heart or continue moving within the venous system through the heart and into the pulmonary arteries. The 7 fractured Bard Recovery filters found on follow-up had been implanted by 3 different physicians, including an interventional radiologist and 2 different general surgeons.

The Bard G2 filter had a lower, but still high, fracture prevalence (12%; 6 of 52). Two of these 6 patients had a fragment embolize cephalad to the IVC, with 1 fragment coming to rest in the hepatic vein and 1 in the lung. Four of the 6 Bard G2 fragmented filters had the fractured strut(s) remain local to the original device implantation location in the IVC (67%). Three different physicians implanted the 6 filters that fragmented, including a vascular surgeon, an interventional radiologist, and a general surgeon.

COMMENT

Complications subsequent to the initial placement of vena cava filters are multiple, and some occur with significant frequency. It is reported that up to 5% of all filters migrate further than 1 cm, with almost all occurrences being asymptomatic.² Perforation or erosion of the filter through the vena cava at the site of implantation is more common³ but is usually without clinical consequence. Fracture of a filter strut has been reported rarely in the literature but has resulted in life-threatening events.^{4,5} In 2 of the cases we found in the literature, the fractured filter fragment embolized to the heart and perforated the right ventricle. In 1 case, the patient had chest pain, and in the second case, the patient had life-threatening cardiac tamponade. Both patients underwent successful emergency open-heart surgery for removal of the fractured filter fragment. The Bard Recovery filter was the implanted device implicated in both of these cases. Hull and Robertson⁶ reported a third patient who had chest pain and nonsustained ventricular tachycardia necessitating removal of fragments from the heart and recovery of the remaining Bard Recovery filter from the vena cava.

Our retrospective review of patients receiving either the Bard Recovery filter or the Bard G2 filter demon-

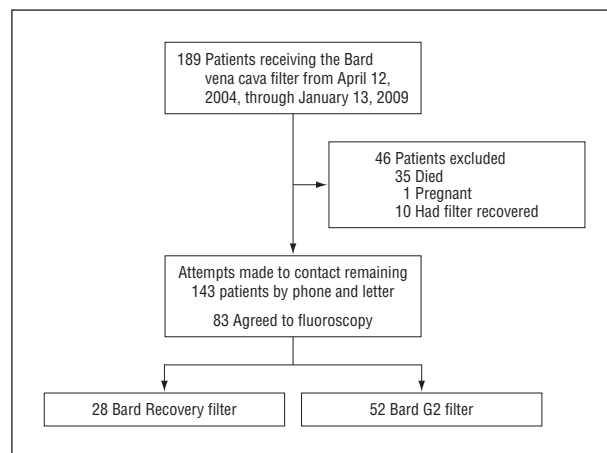


Figure 2. Patient enrollment flowchart. “Recovery” and “G2” are proprietary names of vena cava filters manufactured by Bard Peripheral Vascular, Tempe, Arizona.

strates a high prevalence of fracture of these devices. The Bard Recovery filter had an overall fracture prevalence of 25% (7 of 28). Six of these 7 patients had at least 1 fragment embolize to the heart or beyond to the lungs (86%) (Figure 1), and 3 of the 7 patients experienced life-threatening symptoms. While the Bard G2 filter incorporated engineering modifications to reduce these occurrences, 12% of the implanted Bard G2 filters also fractured (6 of 52). The modifications might have reduced the ability of the fragments to distally embolize—two-thirds of the fragments remained locally within the IVC near the original implantation site—but as demonstrated in patients 10 and 13, the potential for embolization out of the IVC to other vital organs still exists.

The observed prevalence of filter fracture was 25% with the Bard Recovery filter (7 of 28) and 12% in the Bard G2 filter (6 of 52). These data initially suggest that the fracture rate for the Bard G2 filter is approximately half that of the Bard Recovery filter. However, on further analysis, this conclusion may not be accurate. The average time between filter implantation and assessment of filter integrity for the Bard Recovery filter was 1498 days, or approximately 50 months. For the Bard G2 filter, the average time interval was 717 days, or approximately 24 months. The average time intervals in patients where fracture was observed in the Bard Recovery and Bard G2 groups were nearly identical to those of all patients in those respective groups.

Because nitinol metal fatigue may play a role in the filter fracture, it is reasonable to assume that the incidence of filter fracture would be directly proportional to the time that the filter is allowed to dwell in the patient after implantation. Lynch and Kekulawela⁷ reported their experience in removing Bard G2 filters before and after 180 days following implantation. A total of 3.4% of the filters removed had fractured prior to removal, and all fractures were observed in patients who had had the filter implanted for more than 180 days. Cantwell et al⁸ reported a lower observed prevalence of fracture than we observed of the Bard Recovery and Bard G2 filters on removal of the devices, but 95% of the filters in that study were recovered within 15.5 months of implantation.

Table 2. Characteristics of the 13 Patients Found on Fluoroscopy to Have Filter Fragmentation

Patient No./ Age, y	Bard Filter Device ^a	Indication for Implantation	Duration of Implantation, mo	Implanting Physician-No.	No. of Fractured Fragments: No. in Embolization Location	Symptoms
1/78	Recovery	Pulmonary emboli	56	IR-1	3 arms: 2 heart, 1 lung	Palpitations, VPCs and couplets, CP, SOB
2/54	Recovery	Surgery prophylaxis	37	GS-1	3 arms: 3 heart	CP, SOB, tamponade
3/48	Recovery	Surgery prophylaxis	52	GS-2	1 arm: 1 liver	None
4/73	Recovery	Surgery prophylaxis	52	GS-2	2 arms: 1 in each lung	SOB
5/27	Recovery	Malignant neoplasm prophylaxis	51	GS-2	3 arms: 2 heart, 1 lung	None
6/26	Recovery	Trauma	52	IR-2	3 arms and 1 leg: 2 heart, 1 lung, 1 local in IVC	CP, SOB, NSVT
7/63	Recovery	Surgery prophylaxis	44	GS-3	1 arm: 1 heart	CP, NSVT, sudden death
8/21	G2	Trauma	35	VS-1	1 leg: 1 local in IVC	None
9/37	G2	Surgery prophylaxis	29	GS-2	1 leg: 1 local in IVC	None
10/75	G2	Pulmonary emboli	29	GS-2	1 arm: 1 liver	None
11/49	G2	Unknown	18	IR-2	2 legs and 1 arm: all local in IVC	None
12/30	G2	Trauma	10	GS-2	1 leg: 1 local in IVC	None
13/55	G2	Surgery prophylaxis	27	GS-2	1 arm: 1 lung	None

Abbreviations: CP, chest pain; GS, general surgeon; IR, interventional radiologist; IVC, inferior vena cava; NSVT, nonsustained ventricular tachycardia; SOB, shortness of breath; VPCs, ventricular premature contractions; VS, vascular surgeon.

^a"Recovery" and "G2" are proprietary names of vena cava filters manufactured by Bard Peripheral Vascular, Tempe, Arizona.

(mean, 7.5 months). There was a high prevalence of fracture in this short period with the Bard Recovery filter (9%) but no fractures of the Bard G2 filter. Our follow-up periods of 50 months for the Bard Recovery Filter and 24 months for the Bard G2 filter were much longer. These devices are therefore experiencing prolonged exposure to repetitive movement and subsequent metal fatigue, potentially predisposing them to fail.

We would contend that the fracture prevalence seen by Cantwell et al⁸ might have been significantly higher if the filter (which has a permanent implant indication) was allowed to remain in place for a longer period. If one were to extrapolate our observed prevalence of Bard G2 filter fractures to 50 months (essentially double the observed period), the prevalence of fracture would be identical to that observed for the Bard Recovery filter, thus challenging the hypothesis that the Bard G2 filter represents an improvement in fracture resistance.

Of the filters that went on to fracture in our study, 6 different physicians from 3 different disciplines had implanted the devices. While it is possible that our findings may represent a local phenomenon, it is difficult to assert that fracture and fragmentation is an operator-dependent event.

The results of this study point to a difficult clinical challenge to the treating physician advising patients with and without filter fragmentation. Many of the implanted devices are left in place, owing to potential long-term indications for pulmonary embolism prophylaxis. Although the recoverable nature of the filter allows for recovery at a later date, the low rate of recovery in our study is similar to that reported in other series.⁹ As such, the ability to safely remove the device after it experiences local fibrosis into the vena cava may be compromised. It is encouraging that Hull and Robertson⁶ reported 100% successful retrieval of the Bard Recovery filter without complications an average of 899 days after initial implantation in patients requesting Bard Recovery filter removal (12 of 12). In addition, Lynch and Kekulawela⁷ reported a similarly large-volume experience with safe late removal (>180 days after implantation) of the Bard G2 filter.

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The fact that fragment removal from the heart obviously requires open-heart surgery also poses a difficult clinical decision for a physician caring for a patient who has had embolization of fragments to the heart. While echocardiography is useful to determine if a pericardial effusion is present in these patients, absence of effusion at evaluation does not exclude the possibility of its later development or the occurrence of ventricular tachycardia.

Thirty-five of the 189 patients who underwent vena cava filter implantation at our center had died by the time of this study (19%). Indication for filter implantation obviously selects a patient population with a high mortality rate. Twenty-four of the 35 dead patients in our overall population (69%) died either during the hospital stay when the filter was implanted or within 6 months after the implantation.

Reported filter fractures and migration are rare, and it is not a well-known potential clinical complication. Therefore, the clinical suspicion of a filter fracture and migration being the cause of a patient's complaints or symptoms will be low. Patients with perforation of the right heart and tamponade may have shortness of breath, pleuritic chest discomfort, dizziness, and syncope. Death might also result. These are the same symptoms found in patients with pulmonary emboli. One could hypothesize that some patients who might subsequently be seen with presumed symptoms of recurrent pulmonary emboli may in fact have had filter fracture, migration, and perforation.

It is essential that patients and their treating physicians be educated about this previously underrecognized and potentially life-threatening complication of these devices. Armed with this knowledge, educated patients can be alert to the presence of pleuritic chest pain and other symptoms that should prompt immediate evaluation. Such early awareness and evaluation could certainly be life saving. In addition, the propensity for filter fragmentation may be directly related to the duration of implantation. Patients and their physicians

should be educated about this fact so that they have the opportunity to consider having the filter removed.

It is important to recognize that our data represent only a single-center experience. However, 6 different physicians from 3 different specialties implanted the devices that went on to fracture. While our medical center is representative of most large tertiary care hospitals, it is important that our data be corroborated with independent evaluation of implanted devices from other centers. In addition, other brands of IVC filters must be evaluated to determine if our findings are specific to the Bard devices or are a flaw of all such filters.

In conclusion, the prevalence of fragmentation and embolization was found to be high in both the Bard Recovery (25%, 7 of 28) and the Bard G2 (12%, 6 of 52) vena cava filters. Dissemination of these results has a clear benefit for the medical community. Further implantation of these particular devices has been halted at our institution. Educating the medical community and patients on the possibility of device fragmentation and embolization will lead to future patient protection. The optimal approach to the treatment of patients who have already received one of these devices is unclear. Filter fragmentation and embolization might be due to metal fatigue, and therefore its incidence might be directly related to the time that it remains implanted. The decision whether to remove an implanted device will have to be tailored to each individual's particular clinical scenario. It is essential that other medical centers evaluate patients who have received a Bard retrievable filter or any other IVC filter, both for patient safety and to corroborate our single-center findings.

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Author Contributions: Dr W. Nicholson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: W. Nicholson, Goldberg,

and Schuler. Acquisition of data: W. Nicholson, W. J. Nicholson, Tolerico, Taylor, Solomon, Schryver, McCullum, Mills, Shears, Agarwal, and Tuohy. Analysis and interpretation of data: W. Nicholson, Solomon, McCullum, Siddoway, and Tuohy. Drafting of the manuscript: W. Nicholson, Schuler, and Shears. Critical revision of the manuscript for important intellectual content: W. Nicholson, W. J. Nicholson, Tolerico, Taylor, Solomon, Schryver, McCullum, Goldberg, Mills, Siddoway, Agarwal, and Tuohy. Statistical analysis: W. Nicholson and Tuohy. Obtained funding: W. Nicholson. Administrative, technical, and material support: W. Nicholson, Tolerico, Solomon, McCullum, Schuler, Shears, Siddoway, and Tuohy. Study supervision: W. Nicholson.

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INVITED COMMENTARY

HEALTH CARE REFORM

Medical Devices and the FDA Approval Process

Balancing Safety and Innovation

The use of medical devices has greatly increased during the past decade. Indeed, more than 8000 new medical devices are marketed in the United States annually.¹ The US Food and Drug Administration (FDA) is responsible for assuring the safety and effectiveness of devices prior to and following approval for

use in the United States. The FDA classifies medical devices according to risk of causing harm. Class I and II devices are considered to be low risk and approval may be accomplished through a relatively simple "premarket notification" or 510(k) clearance, which does not require clinical data. Class III devices are those consid-